full length thereof, including a polymorphic site shown in Table 1, wherein the polymorphic site within the segment is occupied by a base other than the base shown in Table 1, column 3 ("asn base").

10. (Twice amended) A method of analyzing a nucleic acid comprising;

obtaining the nucleic acid from an individual; and

identifying a base occupying any one of the polymorphic sites shown in Table1 wherein the base is a base other than the base shown in Table 1, column 3 ("asn base").

REMARKS

1. Sequence Listing

Applicants request entry of the substitute sequence listing in adherence with 37 C.F.R. §§1.821 to 1.825. This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-30, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk. The substitute sequence listing corrects the inaccurately entered SEQ ID NO:12 noted by the Examiner in the office action mailed September 11, 2001. In addition, the orientation of SEQ ID NOS: 3-6, 13-20, and 22-29) has been reversed to fulfill requirements under 37 C.F.R. 1.822 (c)(5) to present all nucleotide sequences in the 5' to 3' direction. The information contained in the computer readable disk was prepared through the use of the software program "FastSEQ" and is identical to that of the paper copy. The specification has also been amended to conform to the substitute sequence listing. No new matter is involved.

2. Drawings

Applicants attach 3 sheets of formal drawings.

3. Rejection under 35 USC 112, second paragraph

The Examiner says it is not clear that the reference to a "perfect complement" of a segment in claims 1, 3-9, and 15-33 means perfect complementarity throughout the length of the segment. In response, applicants have further amended the claims for still further clarity. As was noted in the previous response, the

specification inherently discloses perfect complement of the sequences of table 1. Mitochondrial DNA is inherently double stranded, and as with other double-stranded sequences, mitochondrial DNA is conventionally represented by showing only a single strand, it being understood that the other strand is the perfect complement of the strand presented. For simplicity, claim 4 has been amended to depend from claim 1.

4. Rejection under 35 USC 103

Claim 10 stands rejected as anticipated by Anderson. The Examiner says Anderson at p. 462, Table 2 refers to a comparison of the human mitochondrial sequence of several genes with the sequences of bovine mitochondrial DNA. In response, the claim has been amended explicitly to require that the identified base at one of the polymorphic positions is a base other than the base in the Anderson sequence. Anderson does not disclose the identification of alternative bases at the polymorphic positions recited in the present application.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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Reg. No. 37,505

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Fax: (650) 326-2422
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PA 3188949 v1

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning on page 3, line 18, has been amended as follows:

Fig. 1. (A) Design of a 4L tiled array. Each position in the target sequence (upper case) (SEQ ID NO:12) is queried by a set of 4 probes on the chip (lower case), identical except at a single position, termed the substitution position, which is either A, C, G, or T (blue indicates complementarity, red a mismatch). Two sets of probes are shown, querying adjacent positions in the target (SEQ ID NOS:13-20). (B) Effect of change in the target sequence. The probes are the same as in panel A, but the target now contains a single base substitution (C, shown in green) (SEQ ID NO:21). The probe set querying the changed base still has a perfect match (the G probe). However, probes in adjacent sets that overlap the altered target position (SEQ ID NOS:22-29) now have either one or two mismatches (red), instead of zero or one, since they were designed to match the target shown in panel A. (C) Hybridization to a 4L tiled array and detection of a base change in the target. The array shown was designed to the mt1 sequence. (Upper panel) hybridization to mt1. The substitution used in each row of probes is indicated to the left of the image. The target sequence can be read 5' to 3' from left to right as the complement of the substitution base with the brightest signal. With hybridization to mt2 (lower panel), which differs from mt1 in this region by a T $\rightarrow$C transition, the G probe at position 16,493 is now a perfect match, with the other three probes having single base mismatches (A 5, C 3, G 37, T 4 counts). However, at flanking positions, the probes have either single or double base mismatches, since the mt2 transition now occurs away from the query position.

IN THE CLAIMS:

1. (Three times amended) A segment of human mitochondrial DNA or RNA of between 10 and 100 bases including any one of the polymorphic sites shown in Table 1, wherein the polymorphic site within the segment is occupied by a base

other than the base shown in Table 1, column 3 ("asn base") or the perfect complement of the full length of the segment.

4. (Three times amended) An allele-specific oligonucleotide [that is perfectly complementary to a segment of human mitochondrial nucleic acid or its perfect complement including a polymorphic site shown in Table 1, column 1, wherein the polymorphic site within the segment is occupied by a base other than the base shown in Table 1, column 3 ("asn base")] comprising the segment or the full complement thereof as defined by claim 1.

9. (Twice amended) An isolated nucleic acid comprising a segment of at least 10 contiguous bases from SEQ ID NO:30, or the perfect complement of the full length thereof, including a polymorphic site shown in Table 1, wherein the polymorphic site within the segment is occupied by a base other than the base shown in Table 1, column 3 ("asn base").

10. (Twice amended) A method of analyzing a nucleic acid comprising;

obtaining the nucleic acid from an individual; and

[determining] identifying [whether] a base occupying any one of the polymorphic sites shown in Table1 wherein the base is a base other than the base shown in Table 1, column 3 ("asn base").

AMDT/C

SUBSTITUTE SEQUENCE LISTING

<110> Chee et al.
Affymetrix, Inc.

<120> Polymorphisms In Human Mitochondrial DNA

<130> 3028.1

<140> 08/856,376
<141> 1997-05-14

<150> 60/024,206
<151> 1996-08-20

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Figure 1

A

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        tgacatGggctgtag
        tgacatTggctgtag
3'       gacataAgctgtaga
         gacataCgctgtaga
         gacata gctgtaga
         gacataTgctgtaga
```

B

```
5' ..TGAACTGTACCCGACAT..
3'      tgacatAggctgtag
        tgacatCggctgtag
        tgacat ggctgtag
        tgacatTggctgtag
3'       gacataAgctgtaga
         gacataCgctgtaga
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         gacataTgctgtaga
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C

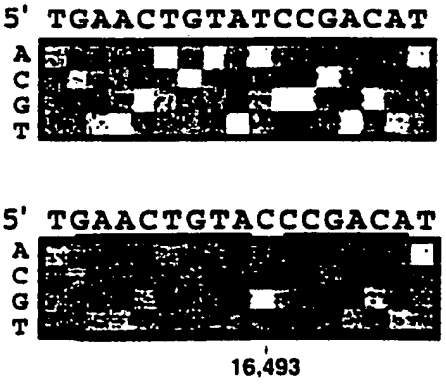
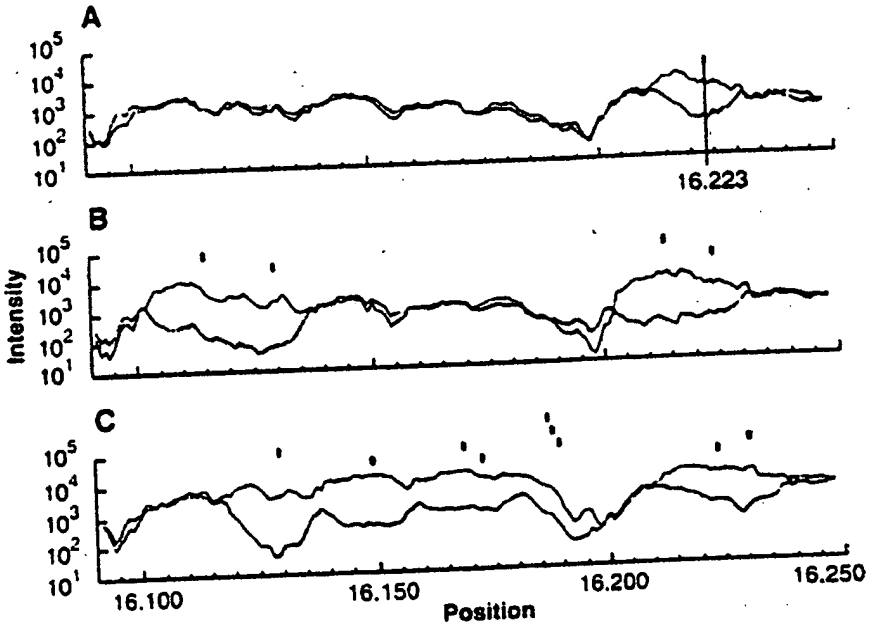


Figure 2


A
B
C
Intensity
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$10^4$
$10^3$
$10^2$
$10^1$
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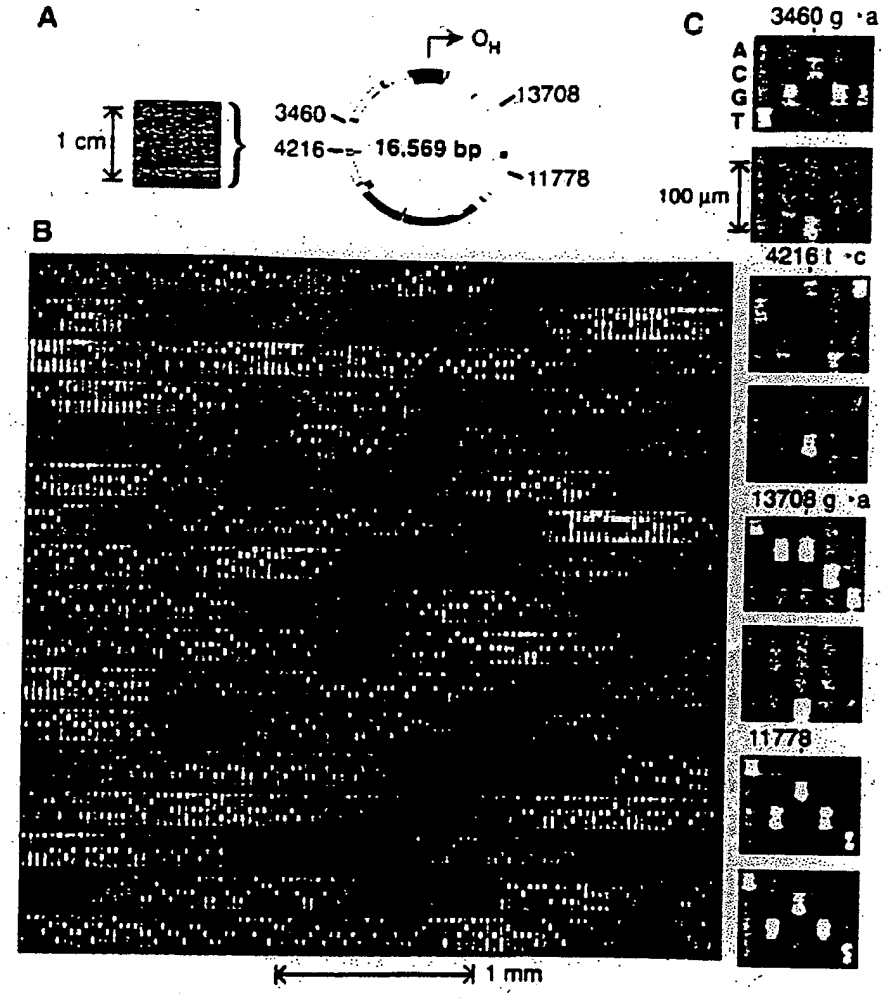
16.100
16.150
16.200
16.250
Position

Figure 3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4216
16,569 bp
13708
11778
B
1 mm
C
3460 g ·a
A
C
G
T
100 µm
4216 t ·c
13708 g ·a
11778